

compound(s) into the microparticles, wherein the lipid based compound(s) are complexed and/or stabilizes the plasmid DNA(s) contained therein.” However, the Examiner asserted that

it would have been obvious for one of ordinary skill in art to employ known lipid based stabilizer/enhance such as those disclosed in Rolland and/or a known lipid based carrier such as those anionic lipid based complex of Lee as a stabilizer and/or are formulated agent of the plasmid vector contained in the microparticles of Mathiowitz or Jones. One of ordinary skill in the art would have been motivated to employ any known lipid based stabilizer and/or agents formulated specifically for plasmid vectors including those disclosed in Rolland and/or Lee, respectively, in order to prepare a condensed plasmid vector for use in the microparticles of Mathiowitz or Jones because Rolland teaches that not only polymeric microparticles containing lipid based stabilizers can be used to enhance and prolong the bioavailability of plasmid vectors encoding a product of interest, the microparticle composition can also be used to do the same with nucleic acid plasmid vectors formulated with a carrier such as a cationic lipid. One then would also have been motivated to employ the lipidic vector based formulation of Lee as a complex with the plasmid vector of Mathiowitz because such lipidic based formulation would function as to reduce plasmid degradation due to its immunogenicity and to enhance transfection activity. One would also have expected from the combined cited references that such enhancements including those driven by a lipid based carrier when complexed with a plasmid vector expressing an antigen would help to increase to stabilize the plasmid vector when circulated *in vivo* or released from the microparticles, thereby enhancing recognition by an immune response to the expressed antigens at a target site such as a mucosal tissue.

Applicants respectfully traverse the rejection in view of the following comments.

Independent claim 1 is directed to a microparticle that less than about 20 microns in diameter and contains: (i) a polymeric matrix; (ii) a lipid; and (iii) a nucleic acid molecule, wherein the microparticle does not contain a liposome or a cell.

As acknowledged by the Examiner, neither Mathiowitz nor Jones describes a microparticle that (1) contains a nucleic acid molecule and a lipid, and (2) is not a liposome. Neither Rolland nor Lee add what is lacking in Mathiowitz and Jones.

Rolland describes compositions and methods for maintaining an administered nucleic acid at a target site so as to increase cellular uptake of the nucleic acid (Rolland at column 1, lines 46-52). Compounds described by Rolland as useful for prolonging the localized bioavailability of an administered nucleic acid include, for example, sustained release compounds, gels, carboxymethylcellulose, polyvinylpyrrolidone, oily suspensions, water-in-oil

microemulsions, and hydrogels (Rolland at column 4, line 35, to column 6, line 26). Nothing in Rolland suggests combining a lipid and a nucleic acid in a non-liposome microparticle.

Rolland's references to lipids and/or oils are in contexts that are unrelated to nucleic acid delivery vehicles such as microparticles (the subject matter of the claimed invention). For example, an "oily suspension" (one of Rolland's several different "compounds which prolong the bioavailability of a nucleic acid") is defined as "a coarse dispersion containing finely divided insoluble material suspended in a liquid medium. These formulations include: nucleic acids, polymers, peptides or sugars and are dispersed with the aid of a dispersing agent, such as a surfactant in a suitable vehicle such as an oil." (Rolland at column 5, lines 56-63; emphasis added). Given that Rolland describes using "oil" as a vehicle for administering bioactive agents such as nucleic acids, polymers, and peptides, the skilled person would have had no scientific rationale for placing such a vehicle (an oil) within a separate delivery vehicle (such as a microparticle) containing a nucleic acid. Placement of such an "oily suspension" within a microparticle would rendered irrelevant Rolland's essential teaching that its compounds function to maintain an administered nucleic acid at a target site so as to increase cellular uptake of the nucleic acid.

Similarly, Rolland's description of phosphatidylcholines (together with a long list of other compounds that are stated to have the ability to prolong the bioavailability of a nucleic acid) does not suggest using phosphatidylcholines with nucleic acids in the context of a polymer-containing microparticle. The skilled person would not have expected that the phosphatidylcholines described by Rolland would carry out their function of maintaining an administered nucleic acid at a target site and facilitate uptake of the nucleic acid if they were contained within a delivery vehicle (e.g., a polymer containing microparticle).

Rolland states that a nucleic acid vector can contain a "transcript stabilizer," which is defined as "a sequence within the vector which contributes to prolonging the half life (slowing the elimination) of a transcript." (Rolland at column 2, lines 21-23). A "transcript stabilizer" is a nucleotide sequence and thus does not encompass lipids.

Lee describes the use of "lipidic vectors" for the delivery of nucleic acids. As is clearly depicted in Fig. 1 (which Figure is described in Lee at column 4, lines 13-15), Lee's "lipidic vector" is a liposome. Furthermore, Lee describes the formation of its liposomes by use of

“helper molecules” (such as CTAB) that contribute a charged species or sequester a charged species in the reaction mixture (Lee at column 6, lines 22-46). According to Lee, such helper molecules can be removed from liposomes following complex preparation by dialysis or gel-filtration chromatography (Lee at column 6, lines 44-46). Claim 1 requires that the microparticle not comprise a liposome. Because liposome compositions, such as those disclosed by Lee, are specifically excluded from claim 1, the use of Lee’s compositions and variants thereof that retain the liposome structure would not result in the claimed microparticle.

In view of the foregoing, the skilled person, as of the filing date of the present application, would have lacked the requisite suggestion or motivation to modify a composition of Mathiowitz or Jones so as to result in the claimed invention. As a result, applicants respectfully request that the Examiner withdraw the rejection of independent claim 1 and claims 2-7 that depend therefrom.

At pages 7-9 of the Office Action, the Examiner rejected claims 8-16, 18-22, 26, 34-36, and 51 as allegedly unpatentable over either Mathiowitz or Jones taken with Rolland and Lee and further in view of either Carson, U.S. Published Application No. 2003/0109469 or Adema, U.S. Patent No. 6,500,919. According to the Examiner,

[t]he combined cited references do not teach explicitly that the immunogenic polypeptide includes a peptide that binds to a MHC class I molecule, that an array of antigenic peptides can be constructed in the plasmid vectors, and that a trafficking sequence can also be linked to the expressed peptide.

However, at the time the invention was made, the concept of employing a peptide or arrays of peptides known in the prior art in a plasmid expression vector for use as an immunogenic composition is taught in Carson. For example, par. 59-60 on page 10-11 discloses that the plasmid vector can be constructed to encode an array of antigenic peptides of choice such as MHC peptides, cytokines, and/or T cell epitopes for tumor treatment, for example. As evidenced by Adema, MHC I binding peptides for use in vaccines such as treatment of a melanoma tumor are well-known in the prior art.

As detailed above in response to the preceding rejection, the combination of Mathiowitz, Jones, Rolland, and Lee does not suggest a microparticle that less than about 20 microns in diameter and contains: (i) a polymeric matrix; (ii) a lipid; and (iii) a nucleic acid molecule, wherein the microparticle does not contain a liposome or a cell. Carson and Adema were cited in

the present rejection as disclosing various immunogenic compositions. However, because the cited references do not render obvious the microparticle of claim 1, it necessarily follows that those claims further limit the nucleic acid contained in the claimed microparticle are also non-obvious. As a result, applicants respectfully request that the Examiner withdraw the rejection of claims 8-16, 18-22, 26, 34-36, and 51.

#### Obviousness-Type Double Patenting

At pages 9-11 of the Office Action, the Examiner rejected claims 1-16, 18-21, 23, 26, 33-36, and 51 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-32 of commonly assigned U.S. Patent No. 5,783,567 ('567 patent) taken with Rolland and Lee and page 40 of the as-filed specification.

Applicants respectfully traverse the rejection in view of the following remarks.

"Obviousness-type double patenting requires rejection of an application claim when the claimed subject matter is **not patentably distinct** from the subject matter claimed in a commonly owned patent when the issuance of a second patent would provide unjustified extension of the term of the right to exclude granted by a patent." MPEP § 804 (emphasis in original). The first inquiry in determining whether there may be a basis for a nonstatutory double patenting rejection is the following: "does any claim in the application define an invention that is merely an obvious variation of an invention claimed in the patent?" Id. If the answer to this question is "yes," then an obviousness-type nonstatutory double patenting rejection may be appropriate. Id.

The microparticles of the claimed invention (1) contain a nucleic acid molecule and a lipid, and (2) are not liposomes.

Nothing in any of claims 1-32 of the '567 patent describes or suggests modifying a microparticle claimed therein to include a lipid but avoid creating a liposome with such a lipid. In addition, for the same reasons as detailed above in response to the rejections under 35 U.S.C. § 103(a), nothing in either Rolland or Lee suggests modifying a nucleic acid-containing microparticle so as to contain a lipid, wherein the new lipid-containing microparticle is not a liposome. Accordingly, the use of a lipid in a microparticle preparation of claims 1-32 of the '567 patent is not merely an obvious variant of those claims. Because the pending claims of

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the present application define inventions that are not obvious variations of an invention claimed in the '567 patent, the issuance of a patent from the present application would not constitute an unjustified extension of the rights granted to the assignee in the '567 patent.

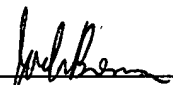
In light of these comments, applicants respectfully request that the Examiner withdraw the rejection.

Conclusions

Enclosed is a Petition for Extension of Time and a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney docket No. 08191-014002.

Respectfully submitted,

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